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Tumor Doubling Time: A Selection Factor for Pulmonary Resection of Metastatic Melanoma

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Background and Objectives: Melanoma patients have a 20–27% rate of 5-year survival after surgical resection of pulmonary metastases. We evaluated tumor doubling time (TDT) and other prognostic factors in an attempt to identify candidates for pulmonary metastasectomy.
Methods: Review of our large melanoma database identified 129 patients who underwent complete or partial resection of pulmonary metastases. At least two preoperative chest roentgenograms were available for 45 patients; these images were used by a single examiner to measure tumor width and length. The mean of the diameters was plotted against time on semilogarithmic paper: the slope of the line approximated tumor growth rate, and TDT was proportional to the inverse of the tumor growth rate.
Results: For the 45 patients with a calculated TDT, median survival was 23.1 months and 5-year survival rate was 15.6% (7/45). By multivariate analysis, the only prognostically significant factors were TDT ($P = 0.006$) and type of pulmonary resection ($P = 0.022$). When TDT was <60 days, median survival was 16.0 months, and 5-year survival rate was zero; when TDT was ≥60 days, median survival was 29.2 months (log-rank test; significant at $P < 0.0001$) and 5-year survival rate was 20.7% (6/29) ($P < 0.0001$).
Conclusions: TDT is the most significant preoperative prognostic factor for patients undergoing pulmonary resection of metastatic melanoma. If TDT is <60 days, a preoperative neoadjuvant regimen of chemotherapy and biologic therapy is recommended. Pulmonary metastasectomy should not be attempted if TDT cannot be increased to ≥60 days by systemic therapy. *J. Surg. Oncol. 1998;69:206–211.*

KEY WORDS: melanoma; neoplasm metastasis; surgery; thoracic; survival

INTRODUCTION

Pulmonary metastasectomy for properly selected patients with American Joint Committee on Cancer (AJCC) stage IV metastatic disease has become increasingly popular. When combining all tumor histologies, several retrospective institutional reviews have reported a 5-year survival rate of 25–48% [1–4] and a 10-year survival rate of 23% [5] in patients undergoing surgical resection of pulmonary metastases.

There is a clear survival advantage associated with resection of isolated pulmonary metastases in patients with metastatic osteogenic sarcoma [6], soft tissue sarcoma [7], nonseminomatous testicular tumors [8], renal cell carcinoma [9], and colorectal carcinoma [10]. In melanoma patients, the reported 5-year survival rate after

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pulmonary metastasectomy for AJCC stage IV disease is 5–31% [11–17]. This wide range indicates the importance of careful patient selection. The literature identifies three preoperative criteria for pulmonary resection: (1) control of the primary tumor, (2) radiological evidence that the patient can be rendered disease-free by surgery, and (3) adequate cardiopulmonary reserve.

Although other preoperative selection criteria are widely discussed, there is no consensus on the importance of the number of pulmonary metastases, the size of the largest pulmonary nodule, the doubling time of the fastest growing nodule, the disease-free interval (DFI) before diagnosis of pulmonary metastases, or postoperative adjuvant therapy. This report examines these potential selection criteria in an attempt to identify which melanoma patients with metastatic disease confined to the lung should be considered for pulmonary metastasectomy.

PATIENTS AND METHODS

From April 1971 through December 1994, 6,509 patients were treated for melanoma by the clinical staff at the John Wayne Cancer Institute (JWCI). Of these, 129 underwent resection of one or more isolated pulmonary metastases. All 129 patients met the following criteria before undergoing pulmonary metastasectomy: (1) complete excision of the primary tumor (if known) with negative surgical margins, (2) no evidence of metastatic disease outside of the thorax, (3) radiographic evidence of surgically resectable intrathoracic disease, and (4) adequate cardiopulmonary status to tolerate the planned operative procedure. Our study population comprised 45 patients whose records included an operative report, a pathology report, and at least two preoperative chest roentgenograms showing visible and measurable pulmonary nodules. Patients with a previously calculated TDT were excluded unless the TDT could be verified by a single examiner (D.W.O.) through measurement of visible metastases on preoperative chest roentgenograms.

Surgical Considerations

The technique for pulmonary metastasectomy has been described previously [18]. Briefly, the operative exposure for pulmonary resection depended on the number and location of metastatic lesions visualized on the preoperative chest imaging studies. If staged posterolateral thoracotomies were used in a patient presenting with bilateral metastases, resection of the least-involved lung was performed first. This enabled the surgeon to determine the extent of surgical resection and the remaining pulmonary volume on the side with fewer lesions before undertaking thoracotomy on the side with more metastases, where a major pulmonary resection–possibly even a pneumonectomy–might be required.

After careful visual inspection and bimanual palpation of the pulmonary parenchyma in both the inflated and deflated conditions, the location of each metastasis was marked with a silk suture. All metastatic lesions were marked prior to resection of any lesion because the resection inevitably resulted in artifacts at the suture line and atelectasis, which can be mistaken for additional lesions. Because the majority of metastatic lesions in the lung are subpleural, a wedge resection was generally used, unless the metastasis was along a fissure. To ensure an adequate margin of normal lung parenchyma surrounding the metastasis (>1 cm for lesions <2 cm, and >2 cm for lesions $\geq$2 cm), and to minimize the incidence of local recurrence at the suture line, Bouie hemorrhoid clamps were placed proximal to the metastasis and the mechanical stapling device was placed beyond the clamps. When multiple wedge resections were not technically feasible, a lobectomy, bilobectomy or pneumonectomy was performed. An ipsilateral mediastinal lymph node dissection was performed after resection of pulmonary parenchymal metastases.

The surgical procedure was curative if all intrathoracic tumor was excised and the pathology reports confirmed tumor-free surgical margins. The surgical procedure was palliative if all intrathoracic disease could not be extirpated and/or the pathology report identified tumor-involved surgical margins.

Tumor Doubling Time

TDT was calculated for each patient by a single investigator (D.W.O.) using a well-described technique [19–21]. Briefly, successive chest radiographs were used to measure the changing diameters of each nodule. On standard 72-inch target-film distance posteroanterior chest roentgenograms, the greatest diameter (length) and the greatest perpendicular diameter (width) of each nodule were measured with a ruler. The mean of the two diameters was then plotted against time on semilogarithmic paper. The slope of the line drawn between the points represented the rate of tumor growth. The horizontal distance between any two doubling points represented the TDT in days [20] (Fig. 1). Because TDT describes the growth rate of the individual nodule used to generate the graph, if a patient had more than one pulmonary metastasis the TDT was determined by the fastest-growing lesion.

Statistical Analysis

Survival time was defined as the number of months from the date of the first pulmonary surgery until death or last follow-up. Estimated survival was calculated by the Kaplan-Meier method. Survival differences were compared according to: (1) age at diagnosis of pulmonary metastasis, (2) gender, (3) anatomical site of primary lesion (extremity vs. trunk vs. head/neck), (4) Clark level (II–III vs. IV–V), (5) Breslow thickness, (6) development

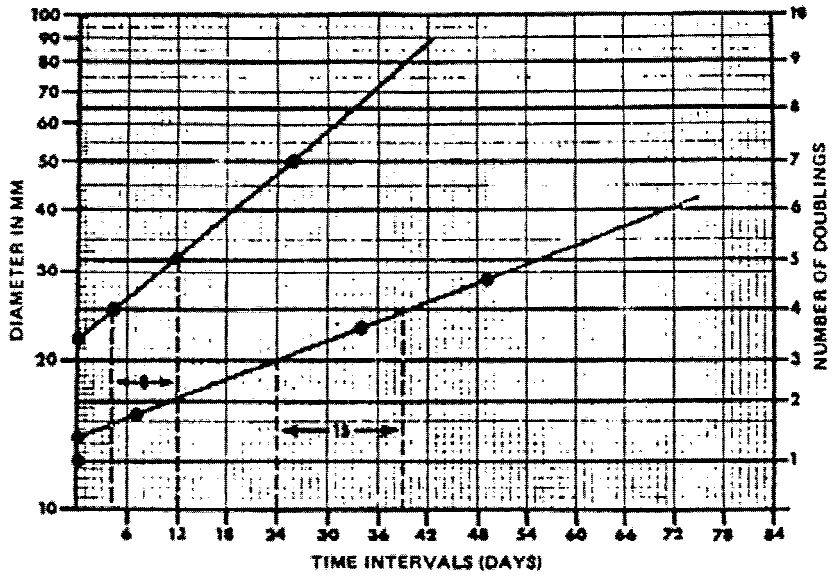

Fig. 1. Calculation of tumor doubling time (TDT) based on direct measurement of the changing diameters of two pulmonary metastases. When more than one metastasis is present, the TDT is determined by the fastest-growing nodule. Reprinted From Joseph et al. [20] with the permission of the Publisher.

of regional nodal metastases prior to diagnosis of AJCC stage IV disease, (7) DFI before diagnosis of stage IV pulmonary disease, (8) number of pulmonary metastases, (9) size of the largest pulmonary nodules, (10) TDT, and (11) type of surgical treatment (curative versus palliative). Age, Breslow thickness, DFI, and the number and size of pulmonary metastases were analyzed as continuous factors; the other factors, including TDT, were analyzed as categorical.

The splitting rule described by LeBlanc and Crowley [22] was used to determine the cut-off point for TDT as a categorical variable. Tree-based methods, in this case classification and regression tree (CART) analysis, are very useful for defining prognostic classifications necessary to interpret data and design clinical trials. The clinician can partition patients into a small number of groups, each associated with a different prognosis. This partitioning maximizes the dissimilarity in survival distributions according to different values of prognostic factors. Dissimilarity is measured with the log-rank test, a well-studied measure commonly used for survival analysis.

Univariate comparisons of survival curves were performed by the log-rank test when the factor was categorical, and by the Cox proportional hazard model when the factor was continuous. SAS PROC LIFETEST® and SAS PROC PHREG® were used for the univariate and multivariate analyses. In all comparisons, statistical significance was determined using an α-level of 0.05 and two-sided tests.

RESULTS

The median age of the 45 patients (30 males, 15 females) was 57.4 years (range 15–76 years). Nineteen patients had intervening nodal metastases (AJCC stage III) before the presentation of pulmonary metastases; the remaining 26 patients had pulmonary metastases as their initial site of metastatic disease. The median DFI from complete resection of either a primary melanoma or regional nodal metastases to presentation with AJCC stage IV pulmonary disease was 15.9 months (range 0–111 months).

Thirty-three patients (73.3%) had a solitary pulmonary metastasis, four patients (8.9%) had two metastases, five patients (11.1%) had three metastases, and three patients (6.7%) had at least four metastases. The mean number of pulmonary metastases per patient was 1.9 (range 1–15). The calculated median TDT for the 45 patients was 66.9 days (range 13.7–287.4 days).

The 42 unilateral thoracotomies and three staged bilateral thoracotomies were accomplished most commonly by pulmonary wedge resection (n = 32, 71.1%), followed in frequency by lobectomy (n = 11, 24.4%) and pneumonectomy (n = 2, 4.4%). Surgery was curative in 38 patients (84.4%) and palliative in the remaining seven patients (15.6%). Of these seven patients, five had extensive unresectable mediastinal involvement that precluded curative resection, one patient required a pneumonectomy but was not a candidate for this procedure, and the remaining patient had intraoperative transdiaphragmatic, biopsy-proven hepatic metastases. There were no operative mortalities. The median overall survival for the 38 patients rendered disease-free was 25.6 months.

Application of the splitting rule [22] identified a TDT value of 60 days as the cut-off point that maximized the dissimilarity of survival distributions for the two patient groups ($P < 0.0001$ by log-rank test). Thus, TDT $\geq$60 days versus <60 days was used as the categorical variable. By univariate analysis (Tables I and II) the only

TABLE I. Metastatic Melanoma: Univariate Analysis: Patient and Primary Tumor Characteristics

Factor	Univariate *P*-value
Age	
Continuous	0.3584
Gender	0.7403
Clark level: II/III, IV/V	0.3106
Breslow thickness: continuous	0.6309
Primary site:	
head/neck	0.7260
extremity	0.8366
trunk	0.7423

TABLE II. Melanoma: Univariate and Multivariate Analysis: Metastatic Tumor Characteristics*

Factor	Univariate *P*-value	Multivariate *P*-value
TDT[a] <60 vs ≥60 days	0.0116	0.0062
Curative vs palliative surgery	0.0471	0.0223
Intervening regional nodal disease	0.8083	—
DFI before lung metastasis: continuous	0.3574	—
Postoperative adjuvant therapy	0.7438	—
Size of largest pulmonary nodule: continuous	0.3939	—

*Cox proportional hazards model.
[a]TDT, tumor doubling time; DFI, disease-free interval.

statistically significant prognostic factors related to overall survival were TDT ≥60 days ($P = 0.0116$) and a curative surgical procedure ($P = 0.0471$). TDT was also significant as a continuous ($P = 0.0019$) variable. For patients with a TDT of <60 days, the median survival was 16.0 months, and only 1 patient survived more than 2 years (31.3 months). For patients with a TDT of ≥60 days, the median survival was 29.2 months and the 5-year survival rate was 20.7% (6 of 29).

When a multivariate analysis was performed, both TDT and a curative surgical procedure remained statistically significant ($P = 0.0062$ and 0.0223, respectively). For those patients who had a TDT of <60 days or who underwent a palliative surgical procedure, the median survival was 17.6 months with no 5-year survivors. For patients with a TDT of ≥60 days who underwent a curative surgical procedure, the median survival was 30.6 months and the 5-year survival rate was 25.0% (5 of 25) (Table III; Fig. 2).

DISCUSSION

Pulmonary metastasectomy for melanoma patients with metastatic disease confined to the thorax has not been embraced with as much enthusiasm as pulmonary metastasectomy for other tumor types. In 1973, Cahan [11] reported an overall 5-year survival rate of 14% for 29 melanoma patients undergoing surgical resection of pulmonary metastases. In 1979, Mathisen and colleagues

TABLE III. Median Survival and 5-Year Survival Rate of Patients With Metastatic Melanoma

Patient group	Median survival (mo)	5-year survival rate (%)
All patients (n = 45)	23.1	15.6
TDT[a] <60 days (n = 16)	16.0	0
TDT ≥60 days (n = 29)	29.2	21.6
TDT <60 days and/or palliative (n = 20)	17.6	0
TDT ≥60 days and curative (n = 25)	30.6	25.9

[a]TDT, tumor doubling time.

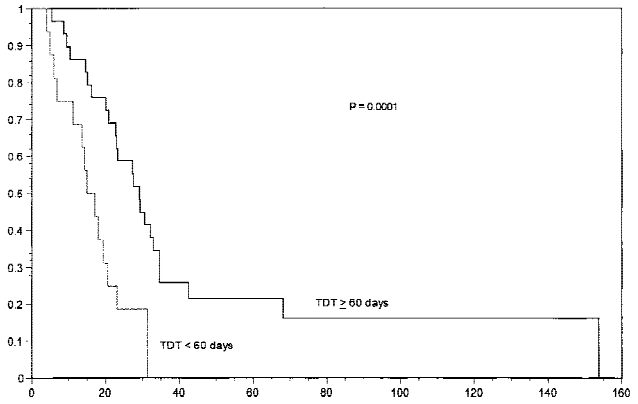

Fig. 2. Survival function estimates according to tumor doubling time (TDT) and type of surgery. Top curve, survival with a TDT of ≥60 and curative surgery; bottom curve, survival with a TDT of <60 and /or palliative surgery.

[23] reported no 5-year survivors and no statistically significant difference in survival rates between patients deemed nonresectable (mean survival 10.5 months) and those surgically rendered disease-free in the lungs (mean survival 12.0 months). Dahlback's group [24] also reported no long-term survivors and concluded that lung surgery did not contribute to the survival of melanoma patients with pulmonary metastases.

Recently, two large institutional reviews demonstrated improved 5-year survival in melanoma patients whose pulmonary metastases were managed surgically. The Duke Comprehensive Cancer Center for Melanoma reported a 20% rate of 5-year survival in 112 patients [16], and the JWCI reported a 5-year survival rate of 27% for 106 patients [17]. The Duke multivariate analysis identified complete pulmonary metastasectomy, prolonged DFI (>12 months) before AJCC stage IV disease, chemotherapy, ≤2 pulmonary nodules, and no intervening AJCC stage III disease as independent prognostic factors contributing to prolonged survival [16], whereas the JWCI multivariate analysis identified TDT and the absence of extrapulmonary metastases as prognostic factors for prolonged survival [17].

As there is no consensus regarding the relative impor-

tance of these other prognostic factors, our univariate analysis included all factors deemed important by other investigators [3–5,12–17]. We found that TDT was the only preoperative factor with prognostic significance. TDT may be an accurate reflection of the ability of the metastatic tumor to replicate and grow within the confines of the pulmonary parenchyma and patient's immune system. If the metastatic clone of tumor cells overwhelms the patient's immune system, the TDT will be rapid. However, if the patient's immune system can exert immunologic control over the metastatic deposit of cells, then TDT will be prolonged.

TDT may be a reflection of the tumor–host interaction, but there is no consensus as to which value of TDT constitutes a favorable/unfavorable prognostic factor. TDT was first described by Collins and colleagues [19] as a method for determining the growth rate of various neoplasms by using serial chest roentgenograms to evaluate the doubling times of metastatic lung lesions. Morton and associates [20,21] were the first to use this method for identifying surgical candidates among patients with pulmonary metastases. They examined pulmonary metastasectomy patients with a variety of primary tumor histologies. All patients with a TDT of <40 days died within 2.5 years, and there was only a 7-month increase in survival beyond that expected from nonoperative management. By contrast, patients whose TDT was >40 days enjoyed a 63% rate of 5-year survival after surgical resection of the metastatic lesion. However, Putnam and colleagues [7] favor 20 days as the criterion for resection in sarcoma patients, and their data confirm that in select patients, TDT is a prognostic indicator that may overrule conventional indicators and criteria. The behavior and operability of the metastatic lesion and the patient's chances of survival thus seem to be a function of tumor growth kinetics and TDT [25].

A previous multivariate analysis from our group identified the prognostic significance of TDT in a sample of only 26 patients [17]. In the present study we examined TDT in 45 patients, still a relatively small population. The fact that the *P*-value was highly significant reinforces the prognostic importance of TDT. The small sample size may also explain why DFI and number of pulmonary nodules were not statistically significant in the present study.

This series represents the largest group of melanoma patients with a calculated TDT managed with pulmonary metastasectomy. The data indicate that pulmonary resection should be considered only in patients with a TDT of ≥60 days. In patients with rapidly growing tumors (TDT <60 days) the likelihood of other foci of rapidly growing metastatic clones is much greater. Therefore, we now recommend preoperative neoadjuvant biochemotherapy (dacarbazine, cisplatin, carmustine, interleukin-2, interferon-α, tamoxifen) for patients with a rapid TDT. If a melanoma patient is not a candidate for pulmonary metastasectomy, biochemotherapy appears to offer the best chance for a complete response. If there is a good partial response or significant slowing of the tumor's growth rate, the patient can be reevaluated for pulmonary resection–an approach similar to that used in selecting sarcoma patients for pulmonary metastasectomy [26].

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